REMARKS

Upon entry of the present amendment, claims 1-9 are canceled, claims 10, 11, 13, and 14 are amended, and claims 15-23 are newly presented. Accordingly, claims 10-23 are presently pending. Of these, claims 11-14 have been withdrawn from consideration subject to the restriction requirement of November 13, 2007.

In an effort to expedite prosecution, Applicants have canceled elected claims 1-6 and 9 and replaced them with new claims 15-23 which more clearly specify that the composition at issue is a medicament for allergen-specific immunotherapy capable of generating an immunoprotective response containing a therapeutically effective amount of microparticles comprising:

(a) a bead consisting of a three-dimensionally cross-linked carbohydrate selected from the group consisting of polyarylamide, vinyl polymer, dextran, agarose, and mixtures thereof; and

(b) a polypeptide allergen derived from plant pollen covalently bound to said bead.

Support for this amendment is found in the as-filed specification, for example at p. 2, lines 10-12; p. 3, lines 6-7; and p. 4, line 12 to p. 5, line 14. However, Applicants reiterate that this amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Pursuant to the Non-Final Office Action of February 21, 2008, elected claims 1-6, 9, and 10 stand rejected on both reference and non-reference grounds. In that claims 1-6 and 9 have been canceled and claim 10 has been amended to depend from new claim 15, Applicants respectfully submit that the instant response renders moot the outstanding claim rejections and places the instant application in condition for allowance. Further to this position, Applicants submit the following remarks:

Rejections Under 35 USC 112, First Paragraph

Enablement:

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. In particular, while the Examiner finds the specification to be enabling for a microparticle consisting essentially of CBP and Phl p 5b, she finds it does not reasonably provide enablement for (a) a microparticle comprising a bead consisting essentially of a three dimensionally cross-linked carbohydrate having an allergen derived from plant pollen (e.g., grass pollen, more particularly timothy grass pollen) covalently bound thereto, or (b) a medicament for the treatment of the immune system comprising such a microparticle. With respect to issue (a), the Examiner asserts that the specification does not adequately disclose any "allergen" for use in the claimed invention, noting that the term "allergen" encompasses non-peptide molecules, such a metals, which would not covalently bind to a three-dimensionally cross-linked carbohydrate. With respect to issue (b), the Examiner asserts that the specification fails to provide enablement for the "treatment of the immune system", noting that the term "treatment" encompasses both positive and negative responses yet a single molecule cannot be used to both enhance and inhibit the same response. The Examiner further challenges whether one could reasonably predict *in vivo* efficacy of the claimed medicament given the limitations of the instant disclosure.

Applicants respectfully submit that the cancellation of claims 1-6 and 9 and the amendment to claim 10 renders moot the instant rejection. Applicants further submit that new claim 15 addresses the Examiner's specific concerns by reciting "a *polypeptide* allergen derived from plant pollen" (thereby excluding non-peptide molecules such as metals) as well as a medicament "for allergen-specific immunotherapy capable of generating an immunoprotective response" (thereby avoiding the alleged contradiction inherent to immune system "treatment"). However, in the event the Examiner's enablement concerns extend to newly presented claims 15-23, Applicants offer the following comments:

The test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The present invention relates to the discovery of the advantageous nature of carbohydrate-based allergen particles over traditional aluminum

hydroxide-based allergen particles in the context of allergen-specific immunotherapy. However, as noted in the instant specification (see, for example, p. 5-6), the coupling of polypeptide allergens to carbohydrate-based particles, such as agarose/sepharose beads, uses well-described and reproducible procedures analogous to those conventional in the art of ELISA-based diagnostic protocols. Likewise, the medicaments of the present invention operate in a manner analogous to conventional Alum-adsorbed allergy vaccines, inducing an allergen-specific IgG response similar to that of Alum-based particles[1]. Accordingly, one of ordinary skill in the art would be well versed in the methods of making and using the medicaments of the present invention, without undue experimentation and with predictable results.

As for the Examiner's request for evidence substantiating the present claims to "medicaments" (now, "medicaments for allergen-specific immunotherapy capable of generating an immunoprotective response" as set forth in new claim 15), Applicants respectfully direct the Examiner's attention to the examples of the instant specification. The experimental results presented herein conclusively demonstrate that the microparticles of the present invention elicit immune responses that are comparable, and indeed superior, to that of aluminum hydroxide, without the associated granulomatous tissue reactions. Not only do the carbohydrate-based medicaments of the present invention induce strong IgG1, IgG2a/b, and IgG3 antibody responses in mice, antibodies referred to as "blocking antibodies" for their ability to prevent contact between the allergen and the IgE molecules present in the allergic patient's body, thereby avoiding mast cell- and basophil-mediated allergic responses such as cytokine secretion and histamine release[2], but they do so with minimal negative side effects, with predictable efficacy of adsorption, with predictable stability of adsorbents, and without altering the functionality of the bound allergen. Thus, it is readily apparent that the medicaments of the instant invention are suited to allergen specific immunotherapy and are capable of generating an immunoprotective response in the subject to be treated.

In sum, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification demonstrate that a reasonable correlation exists between the scope of the

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[1] See e.g., Vrtala et al., *J. Immunol.*, 2000, 165:6653-9, and 1998, 160:6137-40, and, referenced in the instant specification at pp. 8 and 9, respectively.

[2] See Ball et al., *Eur. J. Immunol.*, 1999 29:2026-36 and van Neerven et al., *J. Immunol.*, 1999, 163: 2944-52, reference numbers 28 and 29, respectively, of the Gronlund publication discussed in detail below, which serves as the basis for the instant application.

claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the claims 10 and 15-23 without undue experimentation and with a reasonable expectation of success.

Written Description:

Claims 1-6, 9, and 10 stand rejected further under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. While the Examiner accedes to Applicants' possession of a microparticle consisting essentially of CBP and a Phl p 5b allergen consisting of SEQ ID NO:1, she challenges whether Applicants were in possession of (a) a microparticle comprising a bead consisting essentially of a three dimensionally cross-linked carbohydrate having an allergen derived from plant pollen (e.g., grass pollen, more particularly timothy grass pollen) covalently bound thereto, or (b) a medicament for the treatment of the immune system comprising such a microparticle. According to the Examiner, the disclosure of a single example (i.e., CBP and Phl p 5b) is insufficient to represent the degree of diversity encompassed by the claimed genus.

Applicants respectfully submit that the cancellation of claims 1-6 and 9 and the amendment to claim 10 renders moot the instant rejections. However, in the event the Examiner finds the above concerns to extend to newly presented claims 15-23, Applicants offer the following comments:

The standard for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). The standard for determining sufficiency of the description is "factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *In re Wertheim*, 541 F.2d at 262 (citing *In re Ruschig* 379 F.2d 990, 995-96 (C.C.P.A. 1967)). It is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that the claim encompasses. The law does not require that the specification describe the exact details for preparing each and every species within the genus described. In fact, even if the Examiner considers the subject matter

of the claims to be broader than that disclosed in the original specification, the written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the earlier specification.

Accordingly, possession of a genus may be satisfied through sufficient description of a "representative number of species" wherein the species actually described are representative of the entire genus. When there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation; conversely, when the genus lacks variation, a single species may suffice. What constitutes a representative number is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number of species depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

In this case, Applicants reiterate that the coupling of polypeptide allergens to carbohydrate-based particles, such as agarose/sepharose beads, is conventional in the art of ELISA-based diagnostic protocols. Applicants further submit that the principle mode of allergen-specific immunotherapy does not depend on the nature of a certain allergen but can be readily and routinely generalized for other peptide allergens. Thus, in the context of the instant invention, the timothy grass pollen allergen Phl p 5b (SEQ ID NO:1) is indeed representative of the requisite structural and functional properties of the genus of "polypeptide allergens derived from plant pollen". As for the supporting carbohydrate bead, to expedite prosecution, Applicants have amended the claims to require three-dimensionally cross-linked carbohydrate selected from the group consisting of "polyarylamide, vinyl polymer, dextran, agarose, and mixtures thereof". Not only does this genus that finds explicit support in the instant specification (see p. 2, lines 10-12) but Applicants respectfully submit that it is a genus that lacks substantial variation and of which the CBP bead is sufficiently representative of the distinguishing identifying characteristics common to the species encompassed thereby.

Thus, Applicants respectfully submit that the instant specification provides an adequate written description of the genus of medicaments encompassed by claims 10 and 15-23, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed.

Rejections Under 35 USC 102

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Nordvall et al. (*Allergy*, 1986).

Claims 1-3, 5-6, and 9-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by King et al. (*Clinical Allergy*, 1976).

Claims 1-2, 5-6, and 9-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by van Toorenbergen et al. (*International Archives of Allergy and Immunology*, 2000).

Applicants respectfully submit that these rejections are rendered moot by the cancellation of claims 1-6 and 9 and the amendment of claim 10 to depend from new claim 15. However, in the event the Examiner finds the above concerns to extend to newly presented claims 15-23, Applicants offer the following comments:

The disclosures of Nordvall, King and van Toorenbergen are limited to the diagnostic use of particle bound allergens, i.e., the use of bead-bound allergens to measure allergen specific antibodies for diagnostic purposes. However, none disclose or suggest an administrable medicament for allergen-specific immunotherapy and capable of generating an immunoprotective response, the medicament containing a therapeutically effective amount of microparticles comprising: (a) a bead consisting of a three-dimensionally cross-linked carbohydrate selected from the group consisting of polyarylamide, vinyl polymer, dextran, agarose, and mixtures thereof; and (b) a polypeptide allergen derived from plant pollen covalently bound to said bead as the present claims require. Accordingly, neither Nordvall et al. nor King et al. nor van Toorenbergen et al. anticipates the invention of claims 10 and 15-23 as presented herein.

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Gronlund et al. (*Immunology*, 2002).

Applicants respectfully submit that this rejection is rendered moot by the cancellation of claims 1-6 and 9 and the amendment of claim 10 to depend from new claim 15 as well as the declaration of Dr. Hans Groenlund provided herewith as Appendix A. In order for a

reference to qualify as "prior art" under section 102(a) of 35 U.S.C., it must be by "others". As the instant declaration evidences, the Gronlund et al. publication at issue (i.e., *Immunology*, 107:523-529, 2002) is not a publication by "others" but in fact a publication by the inventors, notwithstanding the inclusion of additional author, Gerhard Dekan. As stated in point 4 of the instant declaration, Gerhard Dekan was merely working under the direction of the present inventors, providing technical assistance, and did not contribute to the conception and/or reduction to practice of the invention disclosed and claimed herein. Thus, in that the Gronlund et al. (Immunology, 2002) publication cited by the Examiner is not in fact "prior art", it cannot serve to anticipate the invention of the pending claims.

Rejection under 35 USC 103

Claims 1 and 3-4 stand rejected under 35 U.S.C. § 103(a) as being obvious over van Toorenbergen et al. in view of Nordvall et al., both of which are discussed above.

Claims 1 and 5-6 stand further rejected under 35 U.S.C. § 103(a) as being obvious over van Toorenbergen et al. or King et al., each in view of Johansen et al. (*European Journal of Pharmaceutics and Biopharmaceutics*, 2000).

Applicants respectfully submit that these rejections are rendered moot by the cancellation of claims 1-6 and 9 and the amendment of claim 10 to depend from new claim 15. However, in the event the Examiner finds the above concerns to extend to newly presented claims 15-23, Applicants offer the following comments:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See M.P.E.P. § 2142, 2143.

The limitations of Nordvall et al., King et al., and van Toorenbergen et al. are discussed above. Applicants respectfully submit that not only does Johansen et al. fail to cure the above-noted deficiencies but in fact presents a number of its own deficiencies. Like the prior art references discussed above, Johansen et al. fail to disclose the use of particle-bound allergens for allergen-specific immunotherapy. Furthermore, Johansen et al. describe microspheres made from a totally different material, namely a poly(lactide) or poly(lactide/glycolipide), neither of which is carbohydrate selected from the group consisting of "polyarylamide, vinyl polymer, dextran, agarose, and mixtures thereof" as the present claims require. In addition, the PLA/PLCA-MS particles described by Johansen et al. release the encapsulated allergen "in a continuous pulsative manner" (see introduction, first paragraph) whereas the carbohydrate bound particles of the present invention must not and in fact do not release the allergen as such would elicit sever systemic allergic side effects. Finally, Table 1 of Johansen et al. states that there are no methods available for measuring antigen contents. However, the carbohydrate bound allergens of the present invention indeed can be readily measured and quantitated; in fact, this is one of the many advantages arising from using carbohydrate beads instead of alum-based particles. Thus, Applicants respectfully submit that none of the references, alone or in combination, render obvious the invention of the presently pending claims.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **May 21, 2008**. In that the Petition for a Two-Month Extension of Time extends this deadline to on or before **July 21, 2008**, Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: July 21, 2008

By: /chalin a. smith/

Smith Patent Consulting, LLC
3309 Duke Street
Alexandria, VA 22314
Telephone: (703) 549-7691
Facsimile: (703) 549-7692

Name: Chalin A. Smith
Title: Attorney for Applicant
Registration No. 41,569

CUSTOMER NUMBER 31,496

Attachments: Appendix A - Declaration of Hans Groenlund